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BIODEGRADABLE IMPLANT MATERIALS

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(54) Title: BIODEGRADABLE IMPLANT MATERIALS

(57) Abstract: A biodegradable implant material, the material comprising anhydrous calcium sulphate in the form of soluble or insoluble anhydrite. The material may be used alone or in combination with a bioresorbable polymer or therapeutic agent.

Biodegradable Implant Materials

This invention concerns biodegradable implant materials, and particularly but not exclusively biodegradable implant materials suitable for medical uses such as bone grafting or bone fixation procedures.

In orthopaedics and oral/maxillofacial surgical applications there is a great need for biocompatible and bioresorbable implant materials which can be conveniently and effectively used either as bone void fillers in non load bearing applications or as bespoke devices for mechanical fixation applications at a bony site.

It is preferable that these implant materials are synthetically derived in order to overcome some of the difficulties and potential problems reported to be associated with allograft or autograft tissue.

For bone void filling in unloaded or lightly loaded applications, synthetic inorganic materials generally comprise either hydroxyapatite, tri-calcium phosphate or calcium sulphate dihydrate.

Many devices for application at a bony site within the body are manufactured from thermoplastic bioabsorbable polymers. These materials offer a number of advantages over traditional metallic devices including; no stress shielding effects; no long term metal ion release, no interference with MRI imaging techniques and no need to remove the implant in a further surgical procedure.

The main mechanism for degradation of this class of polymer within the body is by hydrolysis. The rate of degradation and loss in strength of the polymer can be tailored to suit the clinical indication.

Thermoplastic polymers can be processed into complex net-shaped components in an efficient and cost effective manner by techniques such as injection moulding.

In order to improve the potential of these materials for many orthopaedic and maxillofacial applications, bio-ceramic fillers can be introduced to give biocomposite materials

with properties more appropriate to the clinical need than the polymers or copolymers alone. The fillers may comprise bioactive materials, such as hydroxyapatite (HA) or beta tri-calcium phosphate (β-TCP) in particulate form, which can confer a number of advantages. These materials are osteoconductive and can give the potential for bony in-fill to the surgical site once the polymeric component has been bioabsorbed.

In addition the presence of a filler in a polymer increases its flexural and Youngs modulus such that modulus matching to bone becomes possible. The presence of the filler also imparts a measure of X-ray density to the material which makes imaging a little easier. It has also been demonstrated that these materials present as fillers can provide a buffering action to the acidic degradation products of the polymer, helping to minimise any acidosis effects within the body.

There are essentially three calcium based synthetic crystalline osteoconductive bone graft materials in clinical use. These are used alone or sometimes as mixtures and include hydroxyapatite (HA), beta tri-calcium phosphate (βTCP) and calcium sulphate (CS). The clinical requirement together with the surgeon's preference dictate which grafting material is used.

Hydroxyapatite in crystalline and stoichiometric form is thermodynamically stable in the body and as such is essentially non-resorbing. Beta tri-calcium phosphate is practically insoluble, however within the body at a bony site it is slowly resorbed over a period of several months primarily by cell mediated processes and provides an environment for new bone formation. When these materials are used as fillers within a bio-absorbable polymer they can only become bio-absorbed themselves once the polymer component has started to degrade, resorb and become porous to such an extent that the body's cells have access to said filler component. This process can take many years for the higher strength and higher molecular weight polymers currently used for bony site fixation applications.

Calcium sulphate is used as a bone graft material either in the form of pellets/granules of gypsum ($CaSO_4$. 2 H_2O) or as plaster of paris ($CaSO_4$ ½ H_2O) which is mixed with water or saline to form a paste which subsequently hardens and sets as gypsum. These materials are soluble in water and within the body they are bio-absorbed by a simple dissolution mechanism over a period of 30-60 days. This can be considered to be rather rapid for some applications in a bony site since it is faster than the rate at which new bone can form.

In addition it is impossible to mould the hydrated forms of calcium sulphate into a thermoplastic polymer by melt processing since the processing temperatures for most thermoplastic bio-absorbable polymers are higher than the temperature at which gypsum and plaster of paris lose their combined water. A way to overcome this difficulty would be to dehydrate the gypsum or plaster of paris to give anhydrous calcium sulphate prior to moulding of the components. The reaction and dehydration temperatures are as follows:-

	60°C		100°C	
$CaSO_4.2H_2O$	→	$CaSO_4.\ ½H_2O$	→	$CaSO_4$
gypsum	plaster of paris		soluble anhydrite	

The main problem with the use of the soluble anhydrite as a bioactive filler for a thermoplastic bioabsorbable polymer in a load bearing application is that as water from bodily fluids diffuses into the composite matrix the calcium sulphate solubilises and diffuses out thus leaving pores within the polymer. This occurs in a time period which is short compared to the rate of bony union and to the rate at which the polymer is designed to degrade. The formation of porosity within the polymer is accompanied by a rapid fall in both strength and modulus and hence the polymers ability to maintain mechanical integrity to the healing bone, obviously a major drawback in a load-bearing application. In addition calcium sulphate in the form of gypsum, plaster of paris or soluble anhydrite can give an acidic response when immersed in water, which would contribute to the acidosis effect sometimes reported to be associated with certain bioresorbable polymers.

According to the present invention there is provided a biodegradable implant material, the material comprising anhydrous calcium sulphate.

The material may also comprise bioabsorbable polymer.

The material may also comprise a bioabsorbable calcium phosphate material.

The material is preferably degradable in a body in a similar time frame to the rate at which new bone can form.

The anhydrous calcium sulphate may be in the form of soluble or insoluble anhydrite.

The implant material may additionally comprise any of a protein, a growth factor, an antibiotic, a drug or any other therapeutic agent alone or in combination required to be released in a controlled manner at the surgical site.

The insoluble anhydrite may have been formed by heating soluble anhydrite, and desirably at a temperature of greater than 650°C.

The insoluble anhydrite may have been formed by hydrothermal treatment of gypsum, and desirably at temperatures greater than 300°C.

The soluble anhydrite may be insolubilised by surface coating with a calcium phosphate material.

The implant material may comprise a composite of a bioresorbable polymer and a filler, wherein the filler comprises soluble or insoluble anhydrite.

Alternatively or in addition the filler material may include alpha tri-calcium phosphate.

The polymer component is preferably synthetic, and may comprise a polyester.

The polymer component preferably comprises one or more polymers or co-polymers of lactic acid (L and/or DL), glycolic acid, hydroxybutyric acid, hydroxyvaleric acid, poly dioxanone, poly caprolactone, poly ethylene oxide or poly butylene terephthalate.

The filler preferably has a particle size of substantially less than 100 microns. The filler preferably constitutes between 1% and 50% of the material by weight, and desirably between 20% and 40%.

The material may be a bone graft or bone void filler material in the form of powder, pellets, granules or morsels.

The invention still further provides a component made of a material according to any of the preceding fifteen paragraphs.

The component may comprise any of a screw, pin, plate, tack, suture, wound care patch, spinal spacer, osteotomy wedge, non-woven scaffold for tissue engineering applications or other item usable in surgery and related fields of medicine.

Embodiments of the present invention will now be described by way of example only.

When gypsum is heated to a temperature in excess of approximately 100°C it loses all of its combined water to form soluble anhydrite. On heating to temperatures in excess of approximately 450°C the anhydrous calcium sulphate so formed is converted to a form which is known as insoluble anhydrite. This is characterised both crystallographically and by a reduced solubility when compared to the other forms of calcium sulphate. In addition other changes in the material take place as the calcination temperature is increased further, as shown below.

There is disclosed in Table 1 a relationship between the calcination temperature of gypsum and the pH of the resultant powder when suspended in water. The pH increases as the calcination temperature increases, and becomes alkaline when the calcination temperature exceeds approximately 650°C and the alkalinity increases as the calcination temperature increases.

TABLE 1

Phase	Calcination Temperature	pH of Solution
Gypsum		6.5
Soluble Anhydrite	300°C	6.5
Insoluble Anhydrite	600°C	6.75
Insoluble Anhydrite	650°C	7.0
Insoluble Anhydrite	900°C	9.5
Insoluble Anhydrite	1200°C	11.5

The insoluble anhydrite which has been calcined at temperatures of 650°C or above has the potential for pH buffering of the acidic degradation products of the polymer while being amenable to dissolution mediated resorption in a time frame which can be more closely matched to the rate of degradation of the polymer and the rate of healing and new bone formation.

Alpha tri-calcium phosphate (αTCP) is the high temperature phase of TCP and is formed by calcining beta TCP to temperatures in excess of about 1200°C. It is thermodynamically unstable at room temperature and in the presence of water rapidly converts to a calcium deficient hydroxyapatite according to the following equation:-

$$3Ca_3(PO_4)_2+H_2O=Ca_9(HPO_4)(PO_4)_5OH$$

This material is more soluble than HA or beta TCP. It is osteoconductive and is bio-absorbed through both dissolution and cell mediated processes. Alpha TCP when present as a filler in a bio-absorbable polymer would confer similar advantages to HA or beta TCP but in addition would have the potential to be re-modelled into new bone more rapidly.

Specific examples of biodegradable implant materials according to the invention will now be described.

Examples

Example 1

Gypsum pellets having a cylindrical shape with a diameter of 3 mm and height of 2. 5 mm were heated to 900°C at a heating rate of 50°C/hr and held at temperature for 1 hour prior to cooling. The calcined pellets consisted of insoluble anhydrite and were used as a bone graft substitute material in a bone void filling application.

Example 2

Gypsum powder having a particle size substantially less than 250 microns was heated to 400°C and held for 2 hours at that temperature before cooling to give soluble anhydrite. This powder was insolubilised by soaking in a 0.1 molar sodium orthophosphate solution for a time to give an insoluble surface coating on the powder of calcium orthophosphate. The temperature and time of soaking and concentration of the soluble orthophosphate salt can be adjusted to vary the thickness of the surface coating. This powder was then pressed into pellets using a tablet press to give a material suitable for bony site implantation applications.

Example 3

An insoluble anhydrite powder according to example 1 or an insolubilised soluble anhydrite powder according to example 2 was prepared with a particle size substantially less than 100 microns to be used as a filler in a bioresorbable polymer.

Example 4

Gypsum powder of particle size substantially less than 150 microns was calcined at a temperature of 900°C for 2 hours to form the insoluble anhydrite. This was crushed to give a powder of less than 75 microns which was added to poly L-lactide of molecular weight 200,000 Daltons in the proportions PLLA:CS, 4:1 by weight. The compounded mixture was injection moulded to give bony site implant devices.

Example 5

A mixture of gypsum powder which had been calcined to 1200°C and alpha TCP in the ratio 1:2 parts by weight were crushed to pass a 100 micron aperture sieve and blended into a poly (L-lactide-co-DL-lactide) lactide of molecular weight 300,000 Daltons and L : DL ratio of 70 : 30 molar. The percentage fill was 35% by weight.

The mixture was formed into implantable bony site fixation devices including plates, pins and screws by the techniques of compression moulding, extrusion and injection moulding respectively.

Example 6

Gypsum powder having a particle size of substantially less than 250 microns was heated to a temperature of 800°C and held at temperature for one hour prior to cooling. The insoluble anhydrite so formed was mixed together with bone morphogenic protein in the proportions of anhydrite: protein, 99.95:0.05 by weight. The mixture was pressed into pellets which were subsequently used in a bone grafting procedure to provide a graft material having an enhanced ability to promote new bone formation by the steady and controlled release of the therapeutic agent.

Example 7

Gypsum powder having a particle size of substantially less than 250 microns was hydrthermally treated in an autoclave at 300°C for 1 hour.

The resulting insoluble anhydrite was dried and crushed to give a powder having a particle size substantially less than 100 microns. This powder was used as a material component of a porous bioabsorbable scaffold for cell culture for a tissue engineering application.

There are thus described biologically acceptable and bioabsorbable materials which can be formed into bodily implantable components. The material may constitute a filler in a bioabsorbable polymer which degrades in a similar time frame to the polymer. As the material degrades it provides a slowly soluble source of calcium and sulphate ions.

The particle size of the filler is important. Smaller particles are better from the point of view of improved mechanical properties. The preferred particle size for the filler component is substantially less than 100 microns.

As indicated the filler may comprise an insoluble anhydrite, an insolubilised soluble anhydrite, or a mixture of these components. The filler may also include other materials such as hydroxyapatite or tri-calcium phosphate.

Whilst endeavouring in the foregoing specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

CLAIMS

1. A biodegradable implant material, the material comprising anhydrous calcium sulphate.

2. A material according to claim 1, in which the material also comprises bioabsorbable polymer.

3. A material according to claims 1 or 2, in which the material also comprises a bioabsorbable calcium phosphate material.

4. A material according to any of the preceding claims, in which the material is degradable in a body in a similar time frame to the rate at which new bone can form.

5. A material according to any of the preceding claims, in which the implant material additionally comprises any of a protein, a growth factor, an antibiotic, a drug or any other therapeutic agent alone or in combination required to be released in a controlled manner at the surgical site.

6. A material according to any of the preceding claims, in which anhydrous calcium sulphate is in the form of soluble or insoluble anhydrite.

7. A material according to claim 6, in which the insoluble anhydrite has been formed by heating soluble anhydrite.

8. A material according to claim 7, in which the insoluble anhydrite has been formed by heating soluble anhydrite at a temperature greater than 650°C.

9. A material according to claim 6, in which the insoluble anhydrite has been formed by hydrothermal treatment of gypsum.

10. A material according to claim 9, in which the insoluble anhydrite has been formed by hydrothermal treatment of gypsum, and desirably at temperatures greater than 300°C.

11. A material according to claim 6, in which the soluble anhydrite is insolubilised by surface coating with a calcium phosphate material.

12. A material according to any of the preceding claims 6 to 11, in which the implant material comprises a composite of bioresorbable polymer and a filler, wherein the filler comprises soluble or insoluble anhydrite.

13. A material according to any of the preceding claims, in which the implant material comprises a composite of bioresorbable polymer and a filler, wherein the filler material includes alpha tri-calcium phosphate.

14. A material according to claims 12 or 13, in which the polymer component is synthetic.

15. A material according to claim 14, in which the polymer component comprises a polyester.

16. A material according to claims 12 or 13, in which the polymer component preferably comprises one or more polymers or co-polymers of lactic acid (L and/or DL), glycolic acid, hydroxybutyric acid, hydroxyvaleric acid, poly dioxanone, poly caprolactone, poly ethylene oxide or poly butylene terephthalate.

17. A material according to any of claims 12 to 16, in which the filler has a particle size of substantially less than 100 microns.

18. A material according to any of claims 12 to 17, in which the filler constitutes between 1% and 50% of the material by weight.

19. A material according to claim 18, in which the filler constitutes between 20% and 40% of the material by weight.

20. A material according to any of the preceding claims, in which the material is a bone graft or bone void filler material in the form of powder, pellets, granules or morsels.

21. A component made of a material according to any of the preceding claims.

22. A component according to claim 21, which comprises any of a screw, pin, plate, tack, suture, wound care patch, spinal spacer, osteotomy wedge, non-woven scaffold for tissue engineering applications or other item usable in surgery and related fields of medicine.

23. A biodegradable implant material substantially as hereinbefore described.

24. A component usable in surgery and related fields of medicine, the components being substantially as hereinbefore described.